

9/29/04

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NEWS	5	AUG 02	CAlus and CA patent records enhanced with European and Japan Patent Office Classifications
NEWS	6	AUG 02	The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available
NEWS	7	AUG 27	BIOCOMMERCE: Changes and enhancements to content coverage
NEWS	8	AUG 27	BIOTECHABS/BIOTECHDS: Two new display fields added for legal status data from INPADOC
NEWS	9	SEP 01	INPADOC: New family current-awareness alert (SDI) available
NEWS	10	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	11	SEP 01	New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS	12	SEP 14	STN Patent Forum to be held October 13, 2004, in Iselin, NJ
NEWS	13	SEP 27	STANDARDS will no longer be available on STN
NEWS	14	SEP 27	SWETSCAN will no longer be available on STN
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10688348

9/29/04

=> file registry
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE ENTRY	TOTAL SESSION
0.21	0.21

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DICTIONARY FILE UPDATES: 28 SEP 2004 HIGHEST RN 753424-73-6

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=>
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L1 STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 14:30:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED	0 ITERATIONS	0 ANSWERS
SEARCH TIME: 00.00.01		

FULL FILE PROJECTIONS:	ONLINE	**COMPLETE**
	BATCH	**COMPLETE**
PROJECTED ITERATIONS:	0 TO	0
PROJECTED ANSWERS:	0 TO	0

L2 0 SEA SSS SAM L1

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FULL SCREEN SEARCH COMPLETED - 19 TO ITERATE

100.0% PROCESSED	19 ITERATIONS	14 ANSWERS
SEARCH TIME: 00.00.01		

L3 14 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
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10688348

9/29/04

FULL ESTIMATED COST

155.42

155.63

FILE 'CAPLUS' ENTERED AT 14:30:22 ON 29 SEP 2004
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FILE COVERS 1907 - 29 Sep 2004 VOL 141 ISS 14
FILE LAST UPDATED: 28 Sep 2004 (20040928/ED)

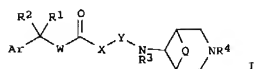
This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3

L4 24 L3

=> d abs bib hitstr 1-24

9/29/04

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
GI

AB Title compds. [I; Ar = (substituted) aryl, heteroaryl; R1 = H, OH, HOCH2, alkyl, amino, alkoxy, cycloalkyl, carbamoyl, halo, aryl; R2 = alkyl, cycloalkyl, cycloalkenyl, (substituted) aryl, heteroaryl; W = (CH2)p; p = 0, 1; X = O, S, NR, null; Y = CH2CO2; R3 = H, Me, (CH2)q; q = 0-4; Q = (CH2)m; m = 0-2; R4 = H, alkyl, CO2CH3; R5 = (unsatd.) (substituted) aliphatic], were prepared. Thus, 5-bromo-4-methylpent-3-ene, (1a,5a,6a)-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane, and K2CO3 were refluxed 5 h in MeCN to give (1a,5a,6a)-N-3-(4-methyl-3-pentenyl)-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane. This was treated with

aqueous HCl in EtOAc at 0° to give (1a,5a,6a)-N-3-(4-methyl-3-pentenyl)-6-amino-3-azabicyclo[3.1.0]hexane. The latter was stirred with 2-hydroxy-2-cyclopentyl-2-(4-methoxyphenyl)acetic acid, hydroxybenzotriazole, N-methylmorpholine, and EDC.HCl in DMF at 0° to room temperature to give (1a,5a,6a)-N-3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]hex-6-yl-2-hydroxy-2-cyclopentyl-2-(4-methoxyphenyl)acetamide. In a contractile assay using rat bladder strips,

T showed pKB = 5.08-8.36 nM.

AN 2004:648506 CAPLUS

DN 141:190686

TI Preparation of 3,6-disubstituted azabicyclohexanes as muscarinic receptor antagonists

IN Mehta, Anita; Silamkoti, Arundutt V.; Kumar, Nareesh; Gupta, Jang Bahadur

PA Ranbaxy Laboratories Limited, India

SO PCT Int. Appl., 115 pp.

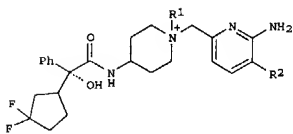
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004067510	A1	20040812	WO 2003-IB256	20030128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,				

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
GI

AB Title compds. I=X- [wherein R1 = (un)substituted alkyl, CH2-alkenyl, CH2-alkynyl; R2 = H, OH; X = anion of a pharmaceutically acceptable acid such as tartaric, HCL, HBr, HI, H2SO4, H3PO4, HNO3, citric, methanesulfonic, benzoic, etc.; and any of their stereoisomers] were prepared as muscarinic receptor antagonists for treating asthma, chronic obstructive pulmonary disorder, allergic rhinitis, and infectious rhinitis. For example, II=I- was prepared by alkylation of the free piperidine with Me iodide in toluene/acetone overnight at 20-25°. Six clin. examples are given. For instance II=I improved the peak flow from 5 l/s to 9 l/s after a week of its administration to a 35 yr old male as a powder at 100 µM once a day.

AN 2004:387264 CAPLUS

DN 140:406738

TI Preparation of quaternary ammonium compounds, in particular piperidinium derivatives, as muscarinic receptor antagonists

IN Heath, Timothy Gordon

PA Pharmacia & Upjohn Company, USA

SO PCT Int. Appl., 16 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004039374	A1	20040513	WO 2003-IB4617	20031017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

L4 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)

ML, MR, NE, SN, TD, TG

PRAI WO 2003-IB256

OS MARPAT 141:190686

IT 738628-36-9P

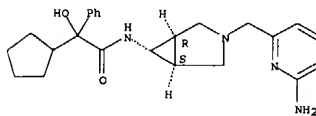
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; preparation of 3,6-disubstituted azabicyclohexanes as muscarinic receptor antagonists)

RN 738628-36-9 CAPLUS

CN Benzeneacetamide, N-[(1a,5a,6a)-3-[(6-amino-2-pyridinyl)methyl]-3-azabicyclo[3.1.0]hex-6-yl]-α-cyclopentyl-α-hydroxy- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004132774 A1 20040708 US 2003-688348 20031017

PRAI US 2002-421962P P 20021029

OS MARPAT 140:406738

IT 688320-38-9P

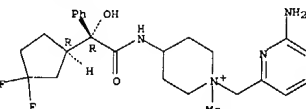
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(muscarinic receptor antagonist; preparation of quaternary ammonium compds., in particular piperidinium derivs., as muscarinic receptor antagonists)

RN 688320-38-9 CAPLUS

CN Piperidinium, 1-[(6-amino-2-pyridinyl)methyl]-4-[[[(1R)-3,3-difluorocyclopentyl]hydroxyphenyl]acetyl]amino]-1-methyl-, iodide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 203321-88-4

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of quaternary ammonium compds., in particular piperidinium

derivs., as muscarinic receptor antagonists)

RN 203321-88-4 CAPLUS

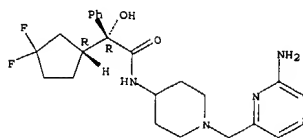
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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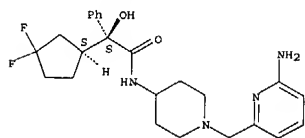
9/29/04

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
RN 476478-92-9 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (4S)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB The possible mechanisms for the chiral recognition of 2- (R)-N-[1-(6-

aminopyridin-2-ylmethyl)piperidin-4-yl]-2- [(1R)-3,3-difluorocyclopentyl]-2-
hydroxy-2-phenylacetamide (RR-M3), and its enantiomer (SS-M3) with
octakis(2,3-di-O-acetyl-6-sulfo)-γ-cyclodextrin (ODAS-γ-CD)
and octakis(6-sulfo)-γ-cyclodextrin (OS-γ-CD), were studied
using capillary electrophoresis (CE), proton (1H), fluorine (19F) and
carbon (13C) NMR spectroscopy (NMR), and IR spectroscopy. Clear evidence
for the formation of diastereomeric complexes between the enantiomers and
the two CDs was observed. NMR spectra suggest that the Ph and
difluorocyclopentyl rings are involved in the complexation. The Ph ring
on the guest mol. is deeply penetrated into the cavity of OS-γ-CD,
but it is not included into the cavity of ODAS-γ-CD. The continuous
variation plots built based on the 1H NMR and IR spectra indicate a 1:1
complex stoichiometric ratio of the M3 enantiomers for both CDs. The
affinity of the enantiomers for the two CDs is opposite.

AN 2003:684003 CAPLUS

DN 139:373801

TI Mechanistic study of the enantiomeric recognition of a basic compound
with

negatively charged single-isomer γ-cyclodextrin derivatives using
capillary electrophoresis, nuclear magnetic resonance spectroscopy, and
infrared spectroscopy

AU Zhou, Lili; Thompson, Richard; Reamer, Robert A.; Lin, Zhihao; French,
Mike; Ellison, Dean; Wyvratt, Jean

CS Merck Research Laboratories, Rahway, NJ, USA

SO Electrophoresis (2003), 24(15), 2448-2455

CODEN: ELCTDN; ISSN: 0173-0835

PB Wiley-VCH Verlag GmbH & Co. KGaA

DT Journal

LA English

IT 203321-88-4 476478-92-9

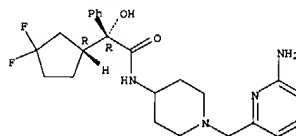
RL: ANT (Analyte); ANST (Analytical study)

(capillary electrophoresis, NMR and IR spectroscopy in mechanistic
study of enantiomeric recognition of aminopyridinylmethylpiperidine
acetamide derivative using neg. charged single-isomer γ-cyclodextrin
deriva.)

RN 203321-88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (4R)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN

AB To investigate whether the inhibition of muscarinic M2 receptors results
in the enhancement of reflex bronchoconstriction under airway
hyperresponsiveness, we evaluated the effects of muscarinic antagonists
with or without M2 antagonist activity on methacholine (MCh)- and
SO2-induced airway responses in ovalbumin (OVA) sensitized and
-challenged

mice. In this model, similar airway hyperresponsiveness to MCh (12
mg/mL)

was observed on Days 31 and 37 (2.2 fold and 2.7-fold, resp.). However,
airway hyperresponsiveness to SO2 (0.05 l/min) on Day 37 was less than
that on Day 31 (4.0- and 2.7-fold on Days 31 and 37), indicating reflex
bronchoconstriction was enhanced on Day 31 in comparison to Day 37.
Ipratropium (0.03 - 0.3 mg/mL, inhalation) and Compound A (0.1 - 3 mg/kg,
p.o.) inhibited MCh-induced responses on Days 31 and 37. Although
ipratropium (0.03 - 1 mg/mL) dose-dependently inhibited SO2-induced
responses on Day 31, ipratropium at a dose of 0.1 mg/mL significantly
increased SO2-induced responses on Day 37 (162.2% of the corresponding
control). On the other hand, Compound A (0.03 - 0.3 mg/kg, p.o.)
inhibited

SO2-induced responses without any increases on Days 31 and 37. These
results suggest that two different conditions of reflex
bronchoconstriction are presented in this model: SO2-induced responses
are

enhanced by dysfunctional M2 receptors on Day 31 while the dysfunctional
M2 receptors are partially restored on Day 37. In addition, the
inhibition

of the restored M2 receptors further enhance reflex bronchoconstriction.

AN 2003:598944 CAPLUS

DN 140:613

TI Effects of muscarinic receptor antagonists with or without M2 antagonist
activity on cholinergic reflex bronchoconstriction in
ovalbumin-sensitized
and -challenged mice

AU Hirose, Hiroyasu; Jiang, Jian; Nishikibe, Masaru

CS Teikoku Research Institute, Banyu Pharmaceutical Co., Ltd., Teikoku,
300-2611, Japan

SO Journal of Pharmacological Sciences (Tokyo, Japan) (2003), 92(3), 209-217

CODEN: JPSTGJ; ISSN: 1347-8613

PB Japanese Pharmacological Society

DT Journal

LA English

IT 203321-88-4

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(effects of muscarinic receptor antagonist activity on cholinergic
reflex bronchoconstriction)

RN 203321-88-4 CAPLUS

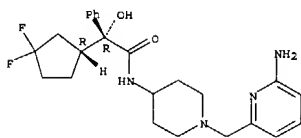
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (4R)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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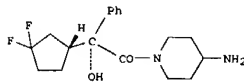
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L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



1

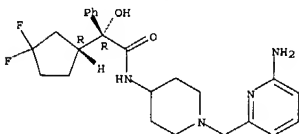
AB Title compds. carrying a variety of diamine moieties without hydrophobic substituent on the nitrogen atom were screened against the binding affinity for the M3 receptor and the selectivity for M3 over the M1 and M2 receptors. This process led to a 4-aminopiperidinamide (I) with a K_i value of 5.1 nM and with a selectivity of the M3 receptor that was 46-fold greater than that of the M2 receptor. Further derivatization of I by inserting a spacer group or by incorporating alkyl group(s) into the amine part resulted in the identification of an 4-(aminomethyl)piperidinamide with a K_i value of 3.7 nM for the M3 receptor and a selectivity for the M3 receptor that was 170-fold greater than that of the M2 receptor.

AN 2003:442757 CAPLUS
DN 139:173181
TI Muscarinic M3 receptor antagonists with (2R)-2-[(1R)-3,3-difluorocyclopentyl] 2 hydroxyphenylacetamide structures. Part 2
AU Ogino, Yoshio; Ohtake, Norikazu; Kobayashi, Kensuke; Kimura, Toshifumi; Fujikawa, Toru; Hasegawa, Takuro; Noguchi, Kazuhito; Mase, Toshiaki
CS Banyu Tsukuba Research Institute (Collaboration with Merck Research Laboratories), Tsukuba, Ibaraki, 300-2611, Japan
SO Bioorganic & Medicinal Chemistry Letters (2003), 13(13), 2167-2172
CODEN: BMCLB8; ISSN: 0960-894X
PB Elsevier Science B.V.
DT Journal
LA English
OS CASREACT 139:173181
IT 203321-88-4
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of fluorocyclopentyl hydroxyphenylacetamides as muscarinic M3 receptor antagonists)

RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[(1R)-3,3-difluorocyclopentyl] α -hydroxy-, (4R)- (9CI)

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



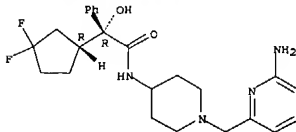
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
AB A review on discussing development of synthetic process for a muscarine M3 receptor antagonist through diastereoselective Michael reaction, selective deoxyfluorination and aromatic metal-halogen exchange reaction, etc.

AN 2003:177129 CAPLUS
DN 139:107641
TI Development of manufacturing process of muscarine M3 receptor antagonist
AU Iida, Takehiko; Mase, Toshiaki
CS Lab. for Synthetic Technology, Banyu Pharmaceutical Co., Ltd., Japan
SO Purosesu Kemisutori no Shintenkai (2003), 238-252 Publisher: Shi Emu Shi Shuppan, Tokyo, Japan.
CODEN: 69DQ2N; ISBN: 4-88231-384-7
DT Conference; General Review
LA Japanese
IT 203321-88-4P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(development of manufacturing process of muscarine M3 receptor antagonist)

RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl] 4-piperidinyl]- α -[(1R)-3,3-difluorocyclopentyl]- α hydroxy-, (4R)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



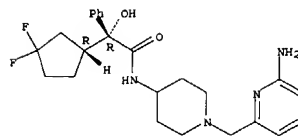
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9/29/04

L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
 AB The simultaneous enantiosepn. of a basic drug compound, 2(R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (M3), and its chiral acidic intermediate, (R,R)-1-(2,2-difluorocyclopentyl)-phenylacetic acid (MA), was investigated by capillary electrophoresis (CE) with various cyclodextrins (CDs). After an initial screening, a single-isomer CD, octakis(2,3-diacetyl-6-sulfo)-gamma-CD (ODAS-gamma-CD), was selected for further method development based on separation selectivity and the peak migration time. Other method parameters such as pH of background electrolyte (BGE), type of capillary, temperature, and organic modifier were varied to optimize the method. The optimal method was validated in terms of linearity, sensitivity, precision, ruggedness, and specificity. A mixture of enantiomers of M3 and MA were spiked into a matrix of reagents used for the synthetic step and the resulting solution was evaluated by the optimized CE-chiral method. The results indicate both pairs of M3 and MA enantiomers were free of interference from the reaction matrix. Therefore, the feasibility of utilizing the method to monitor possible enantio-conversion during the synthetic process was demonstrated.
 AN 2003:11675 CAPLUS
 DN 139:202627
 TI Simultaneous enantioseparation of a basic drug compound and its acidic intermediate by capillary electrophoresis
 AU Zhou, Lili; Thompson, Richard; French, Mike; Ellison, Dean; Wyvratt, Jean
 CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA
 SO Journal of Separation Science (2002), 25(15-17), 1183-1189
 CODEN: JSSCOJ; ISSN: 1615 9306
 PB Wiley-VCH Verlag GmbH & Co. KGaA
 DT Journal
 LA English
 IT 203321-88-4
 RL: ANT (Analyte); ANST (Analytical study)
 (simultaneous enantiosepn. of a basic drug compound and its acidic intermediate by CE)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-alpha-[(1R)-3,3-difluorocyclopentyl]-alpha-hydroxy-, (αR)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

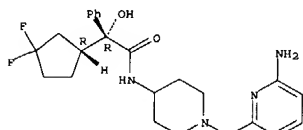
L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)



RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
 AB The enantiosepn. of a weakly basic pharmaceutical drug substance was investigated using sulfated-beta-CD as a chiral selector. The enantiomers are separated at acidic pHs in an anodic flow due to complexation with sulfated-beta-CD, while under an electroosmotic flow (EOF) counter-current. At basic pHs, the EOF prevails and the analytes migrate toward the cathode, where improved sepn. can be obtained along with an apparent reversal of migration order. The optimal enantiosepn. of the test compound was systematically explored by varying important factors, such as pH, concentration of sulfated-beta-CD, temperature, and addition of organic modifier. The implications of the results on general enantiosepn. of weakly basic pharmaceutical compds. were discussed.
 AN 2002:942501 CAPLUS
 DN 139:90581
 TI Enantiomeric separation of a drug substance using capillary electrophoresis with sulfated-beta cyclodextrin
 AU Yuan, Huimin; Thompson, Richard A.; Ellison, Dean K.
 CS Analytical Research Department, Merck Research Laboratories, Merck and Co., Inc., Rahway, NJ, 07065, USA
 SO Journal of Liquid Chromatography & Related Technologies (2002), 25(19), 2999-3015
 CODEN: JLCTFC; ISSN: 1082-6076
 PB Marcel Dekker, Inc.
 DT Journal
 LA English
 IT 203321-88-4 476478-92-9
 RL: ANT (Analyte); ANST (Analytical study)
 (enantiomeric separation of J-104129 pyridinyl difluorocyclopentyl derivative by capillary electrophoresis using sulfated-beta-cyclodextrin as chiral selector)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-alpha-[(1R)-3,3-difluorocyclopentyl]-alpha-hydroxy-, (αR)- (9CI)
 (CA INDEX NAME)

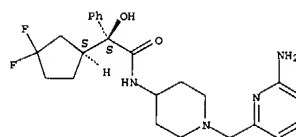
Absolute stereochemistry. Rotation (+).



RN 476478-92-9 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-alpha-[(1R)-3,3-difluorocyclopentyl]-alpha-hydroxy-, (αR)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)



RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

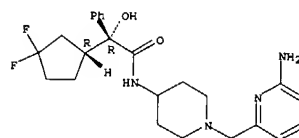
10688348

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L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB Male rats were treated with a muscarinic receptor antagonist at 3, 10,
 and 100 mg/kg/day for 4 wk prior to mating with untreated females and their
 reproductive status was determined on gestation days (GD) 15-17.
 Treatment-related decreases in the pregnancy rate were observed at 100
 mg/kg/day without any effects on mating performance. Impairment of male
 fertility by this compound was also observed after treatment for 1 wk,
 but there were no effects after a 1-wk withdrawal period suggesting
 reversibility of the effect. There were no treatment-related effects on
 sperm production or motility, or testicular histopathol. in any group.
 In order to determine whether the reduced fertility was a class effect of
 muscarinic receptor antagonists, atropine was examined. Males received
 atropine for 1 wk at 62.5 and 125 mg/kg/day and were mated with untreated
 females. A low pregnancy rate associated with a decrease in the number
 of implantations was observed at 125 mg/kg/day. The effect on implantation
 was also observed at 62.5 mg/kg/day. These findings suggest that the
 impairment of fertility in male rats induced by muscarinic receptor antagonists is a
 class effect, and has a relatively short onset of effect and is quickly
 reversible.
 AN 2002:804224 CAPLUS
 DN 138:395946
 TI Impairment of male fertility induced by muscarinic receptor antagonists
 in rats
 Ban, Yoshiaki; Sato, Takahiro; Nakatsuka, Toshio; Kemi, Masayuki; Samura,
 Keiji; Matsumoto, Hiroyoshi; Cukierski, Mark A.; van Zwieten, Matthew J.
 CS Safety Assessment, Banyu Pharmaceutical Co., Ltd., Menuma-machi,
 Osato-gun, Saitama, 360-0214, Japan
 SO Reproductive Toxicology (2002), 16(6), 757-765
 CODEN: REPTED; ISSN: 0890-6238
 PB Elsevier Science Inc.
 DT Journal
 LA English
 IT 203321-88-4
 RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of
 action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU
 (Therapeutic use); BIOL (Biological study); USES (Uses)
 (impairment of male fertility induced by muscarinic receptor
 antagonists)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
 n-[(1R)-2,3-difluorocyclopentyl]-a-hydroxy-, (aR) (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

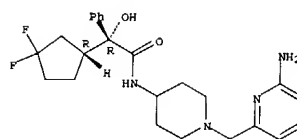


RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB The authors evaluated in vivo functional selectivity profiles for
 muscarinic M2 and M3 subtypes of four muscarinic antagonists: Compound A
 (a novel muscarinic receptor antagonist with M2-sparing antagonistic
 activity), darifenacin, (a muscarinic M3 receptor antagonist), and tolterodine (a
 methoctramine (a muscarinic M2 receptor antagonist) and tolterodine (a
 nonselective muscarinic receptor antagonist), and compared the inhibition
 potency on distention-induced bladder contraction in rats. In an in vivo
 functional study, Compound A (0.03-10 mg/kg, i.v.) showed antimuscarinic
 activity with high selectivity for M3 (salivation) over M2 (bradycardia)
 (>100-fold). Darifenacin (0.01-0.3 mg/kg, i.v.) showed only slight
 selectivity for M3 over M2 (3.7 fold). Methoctramine (0.003-1 mg/kg,
 i.v.) showed the reverse selectivity profile (0.077-fold). Tolterodine
 (0.003-0.3 mg/kg, i.v.) showed less selectivity (1.2-fold). Compound A
 at M3 inhibitory doses (0.1 and 0.3 mg/kg, i.v.) showed inhibition in a
 distention-induced neurogenic bladder contraction model, and its maximal
 inhibitory effects were about 60% at an even higher dose (3 mg/kg).
 Methoctramine at M2 inhibitory doses (0.03 and 0.1 mg/kg, i.v.) did not
 significantly affect distention-induced bladder contraction. When
 tolterodine and darifenacin caused inhibition of distention-induced
 bladder contraction, its maximal inhibitory effects were similar to that
 of Compound A. Therefore, these findings suggest that Compound A would
 be an excellent pharmacol. tool to give a better understanding of which
 subtypes of muscarinic receptors act in bladder function so far, and muscarinic
 M3, but not M2, receptors mainly mediate the cholinergic component of
 distention-induced bladder contraction.
 AN 2002:725247 CAPLUS
 DN 138:66945
 TI The subtypes of muscarinic receptors for neurogenic bladder contraction
 in rats
 AU Hirose, Hiroyasu; Aoki, Ikuo; Kimura, Toshifumi; Fujikawa, Toru;
 Numazawa, Tomohige; Sasaki, Kaori; Nishikibe, Masaru; Noguchi, Kazuhito
 CS Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Ibaraki,
 Tsukuba, 300-2611, Japan
 SO European Journal of Pharmacology (2002), 452(2), 245-253
 CODEN: EJPHAZ; ISSN: 0014-2999
 PB Elsevier Science B.V.
 DT Journal
 LA English
 IT 203321-88-4
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
 BIOL (Biological study)
 (muscarinic receptors subtypes for neurogenic bladder contraction in
 rat)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
 n-[(1R)-2,3-difluorocyclopentyl]-a-hydroxy-, (aR) (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

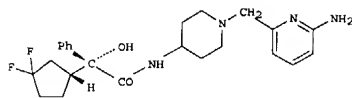


RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
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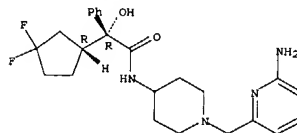
AB The purpose of the following investigation was to display the utility of 19F solid state NMR in both distinguishing between solid forms of a selective muscarinic M3 receptor antagonist (I) and characterizing the active pharmaceutical ingredient in low-dose tablets. Ambient- and elevated-temperature solid-state 19F fast (15 kHz) magic-angle spinning (MAS) NMR expts. were employed to obtain desired spectral resolution in this system. Ambient sample temperature combined with rotor frequencies of 15 kHz provided adequate 19F peak resolution to successfully distinguish crystalline and amorphous forms in this system. Addnl., elevated-temperature 19F MAS NMR further characterized solid forms through 19F resonance narrowing brought about by the phenomenon of solvent escape. Similar solvent dynamics at elevated temps. were utilized in combination with ambient-temperature 19F MAS NMR anal. to provide excipient-free spectra to unambiguously identify the active pharmaceutical ingredient (API) conversion from crystalline Form I to the amorphous form in low dose tablets. It is shown that 19F solid-state NMR is exceptionally powerful in distinguishing amorphous and crystalline forms in both bulk and formulation samples.

AN 2002:501965 CAPLUS
DN 138:243022
TI 19F solid-state NMR spectroscopic investigation of crystalline and amorphous forms of a selective muscarinic M3 receptor antagonist, in both bulk and pharmaceutical dosage form samples

AU Wenslow, Robert M.
CS Merck Research Laboratories, Merck and Co., Rahway, NJ, 07065-0900, USA
SO Drug Development and Industrial Pharmacy (2002), 28(5), 555-561
CODEN: DDIPDS; ISSN: 0363-9045
PB Marcel Dekker, Inc.
DT Journal
LA English
IT 203321-88-4
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES

L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)
(Uses)
(19F solid-state NMR spectroscopic investigation of cryst. and amorphous forms of muscarinic M3 receptor antagonist)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[[1R]-3,3-difluorocyclopentyl]- α -hydroxy-, (aR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN

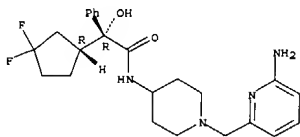
AB The chiral separation of an M3 antagonist was investigated using capillary electrophoresis (CE) with various sulfated cyclodextrins and by reversed-phase liquid chromatog. with derivatized cellulose, derivatized amylose, and two protein stationary phases. Operational parameters for each technique, such as the concentration of the chiral selectors, background electrolyte (or mobile phase) pH and type, organic modifiers, injection mode and temperature were varied in order to achieve a desired elution order and to meet a 0.1% limit of quantitation (LOQ) criteria. Based on the advantages and disadvantages of each technique, a practical CE method using sulfated γ -cyclodextrin was selected. The method was validated in terms of linearity, LOQ, accuracy, ruggedness and precision.

AN 2002:417481 CAPLUS
DN 138:8443
TI Comparison of capillary electrophoresis and reversed-phase liquid chromatography for determination of the enantiomeric purity of an M3 antagonist

AU Song, S.; Zhou, L.; Thompson, R.; Yang, M.; Ellison, D.; Wyvratt, J. M.
CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA
SO Journal of Chromatography, A (2002), 959(1-2), 299-308
CODEN: JCRAEY; ISSN: 0021-9673
PB Elsevier Science B.V.
DT Journal
LA English
IT 203321-88-4 476478-92-9
RL: ANT (Analyte); ANST (Analytical study)
(determination of enantiomeric purity of an M3 antagonist by capillary electrophoresis and reversed-phase liquid chromatog.)

RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[[1R]-3,3-difluorocyclopentyl]- α -hydroxy-, (aR)- (9CI)
(CA INDEX NAME)

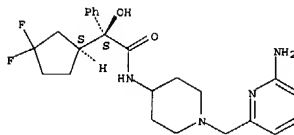
Absolute stereochemistry. Rotation (+).



RN 476478-92-9 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[[1S]-3,3-difluorocyclopentyl]- α -hydroxy-, (aS)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)



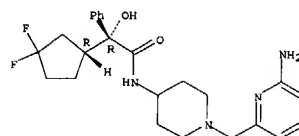
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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9/29/04

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB Investigations on compound A, an M2-sparing M3 muscarinic receptor antagonist, showed that focal polar anterior subcapsular lenticular opacities, characterized by focal epithelial proliferation, developed in Sprague-Dawley rats. The incidence and bilateral localization of this change increased generally with dose and time, though plateauing after 8 mo of treatment; however the severity progressed very slightly. Over a 1-yr period, no anterior cortical lens fiber changes or other histol. ocular changes developed. A decreased severity of the change and apoptosis suggested some regression after a 26-wk recovery period. Two nonselective muscarinic receptor antagonists, atropine and tolterodine, induced similar lenticular changes in rats. A hypothesis in relation to an indirect effect of the drug, such as increased illumination of the lens due to mydriasis observed with all these compds., was investigated and disproven. Because these opacities are induced by structurally unrelated muscarinic receptor antagonists (atropine and tolterodine), it is likely that these lenticular changes are the result of muscarinic receptor inhibition. However, hypotheses regarding a direct effect of the drug on muscarinic receptors in the lens epithelium, possibly mediated by drug and/or metabolite(s) in the aqueous humor and/or lens epithelium, remain to be investigated. This lenticular opacity is similar to that observed spontaneously in Sprague-Dawley rats, although the latter occur at a lower incidence. No such lenticular opacities have been reported in other animal species, including man, after treatment with muscarinic receptor antagonists.
 AN 2002:203384 CAPLUS
 DN 137:41691
 TI Muscarinic receptor antagonist-induced lenticular opacity in rats
 AU Durand, Genevieve; Hubert, Marie-Francoise; Kuno, Hiroshi; Cook, William O.; Boussiquet-Leroux, Christine; Owen, Roger; Fujimaki, Yukio; Kemi, Masayuki; Virat, Michel; Van Zwieten, Matthew J.
 CS Laboratoires Merck Sharp and Dohme Chibret, Clennont-Ferrand, 63963, Fr.
 SO Toxicological Sciences (2002), 66(1), 166-172
 CODEN: TOSCF2; ISSN: 1096-6080
 PB Oxford University Press
 DT Journal
 LA English
 IT 203321-88-4
 RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BICL (Biological study); USES (Uses) (muscarinic receptor antagonist-induced lenticular opacity in rats)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
 (CA INDEX NAME)
 Absolute stereochemistry. Rotation (+).

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

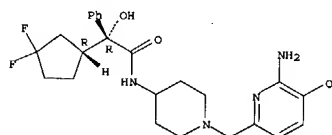


RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

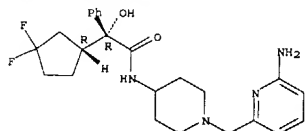
L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB A sensitive, specific, and robust liquid chromatog. (LC)/mass spectrometry (MS)/MS method was developed and validated for a novel M3 muscarinic receptor antagonist (I) and its active 5-OH metabolite (II) in human plasma. The assay involves a two-step liquid liquid extraction of the compds. from human plasma, HPLC separation, and MS/MS for the detection of the analytes. The method provides a linear response from a quantitation limit of 0.05-20 ng/mL for I and 0.1-20 ng/mL for II using 1 mL of plasma. The mean absolute recovery was 85.4% for I and 80.8% for II, resp. The intra-assay accuracy of I and II averaged from 95.0 to 105.3% with coefficient of variation (CV) values 56.5% over the standard curve range. The stability study showed that I and II are stable in the plasma matrix over a period of 11 mo at 70°. The accuracy, ruggedness, and reproducibility of this method were demonstrated by analyzing over 5000 plasma samples in clin. pharmacokinetic studies over a 6-mo period.
 AN 2002:89423 CAPLUS
 DN 137:134
 TI Simultaneous determination of a novel M3 muscarinic receptor antagonist and its active 5-OH metabolite in human plasma using liquid chromatography/tandem mass spectrometry
 AU Yan, Kerri X.; Song, Hengchang; Riffel, Kerry; Lo, Man-Wai
 CS Department of Drug Metabolism, Merck Research Laboratories, West Point, PA, 19486, USA
 SO Journal of Pharmaceutical and Biomedical Analysis (2002), 27(5), 699-709
 CODEN: JPRADA; ISSN: 0731-7085
 PB Elsevier Science B.V.
 DT Journal
 LA English
 IT 203321-88-4 433211-57-5
 RL: ANT (Analyte); ANST (Analytical study) (simultaneous determination of a novel M3 muscarinic receptor antagonist and its active 5-OH metabolite in human plasma using liquid chromatog./tandem mass spectrometry)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
 (CA INDEX NAME)
 Absolute stereochemistry. Rotation (+).

L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 RN 433211-57-5 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-5-hydroxy-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

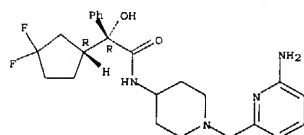


10688348

9/29/04

L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB Enantioselective synthesis of basic pharmaceutical compounds were investigated using different types of sulfated cyclodextrins as chiral selectors. A general strategy for method development was described, together with enantiomeric separation of a number of pharmaceutical related compounds. Based on this strategy, systematic method development approaches for several selected compounds were performed by modifying method parameters, such as the concentration of the chiral selectors, buffer pH, type of organic modifiers, buffer type, temperature and applied voltage. The results of the investigation elucidated the separation mechanism. Many practical aspects were also discussed through several specific examples in order to demonstrate how to develop and validate a precise, sensitive, accurate and rugged separation.
 AN 2002:2310 CAPLUS
 DN 136:406973
 TI A strategic approach to the development of capillary electrophoresis chiral methods for pharmaceutical basic compounds using sulfated cyclodextrins
 AU Zhou, Lili; Thompson, Richard; Song, Sherry; Ellison, Dean; Wyvratt, Jean M.
 CS Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065, USA
 SO Journal of Pharmaceutical and Biomedical Analysis (2001), Volume Date 2002, 27(3-4), 541-553
 CODEN: JPBADA; ISSN: 0731 7085
 PB Elsevier Science B.V.
 DT Journal
 LA English
 IT 203321-88-4
 RL: ANT (Analyte); ANST (Analytical study)
 (strategic approach to development of capillary electrophoresis chiral methods for pharmaceutical basic compounds using sulfated cyclodextrins)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[(1R)-3,3-difluorocyclopentyl]- α -hydroxy-, (9R)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



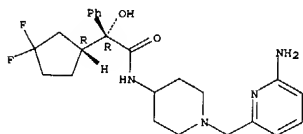
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 AB An improved and efficient synthesis for the preparation of 2-amino-6-[(4-aminopiperidin-1-yl)methyl]pyridine, an intermediate compound in the preparation of muscarinic M3 receptor antagonists, includes as a final step the removal of trimethylacetyl and an amino protecting group from 2-trimethylacetyl-amino 6-[(4-protected aminopiperidin-1-yl)methyl]pyridine. Also prepared was (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
 AN 2001:906225 CAPLUS
 DN 136:37520
 TI Process for the preparation of piperidine derivatives
 IN Maligres, Peter E.; Lee, Jaemoon
 PA USA
 SO U.S. Pat. Appl. Publ., 8 pp.
 CODEN: USXXCO
 DT Patent
 LA English
 FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2001051727	A1	20011213	US 2001-799440	20010305
US 6469172	B2	20021022		
PRAI US 2000-187816P	P	20000308		
OS CASREACT 136:37520; MARPAT 136:37520				
IT 203321-88-4P				

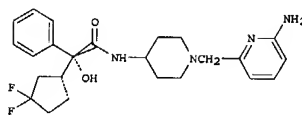
 RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 (preparation of piperidine derivate.)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino 2 pyridinyl)methyl]-4 piperidinyl]- α -[(1R)-3,3-difluorocyclopentyl]- α -hydroxy-, (9R)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 GI



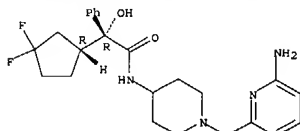
AB An efficient synthesis of a structurally unique, novel M3 antagonist 1 is described. 1 is conveniently disconnected retrosynthetically at the amide bond to reveal the acid portion and the amine fragment. The synthesis of the acid key intermediate is highlighted by a ZnCl₂-MAEP complex catalyzed diastereoselective Michael reaction of a dioxolane with 2-cyclopenten-1-one to establish the contiguous quaternary tertiary chiral centers and a subsequent geminal difluorination of a ketone using DeoxoFluor in the presence of catalytic RF3-OBt₂. The synthesis of the amine moiety is highlighted by the discovery of a novel n-Bu₃MgLi magnesium-halogen exchange reaction for selective functionalization of 2,6-dibromopyridine. This new and practical metalation protocol obviated cryogenic conditions and upon quenching with DMF gave 6-bromo-2-formylpyridine in excellent yield. Further transformations afforded the amine fragment via reductive amination, Pd-catalyzed aromatic amination, and deprotection. Finally, the highly convergent synthesis of 1 was accomplished by coupling of the two fragments. This synthesis has been used to prepare multi-kilogram quantities of the bulk drug.
 AN 2001:653072 CAPLUS
 DN 135:357830
 TI Synthesis of a Muscarinic Receptor Antagonist via a Diastereoselective Michael Reaction, Selective Deoxyfluorination and Aromatic Metal-Halogen Exchange Reaction
 AU Mase, Toshikazu; Houpis, Ioannis N.; Akao, Atsushi; Dorziotis, Ilias; Emerson, Khateeta; Hoang, Thao; Iida, Takahiko; Itoh, Takahiro; Kamei, Keisuke; Kato, Shinji; Kato, Yoshiaki; Kawasaki, Masashi; Lang, Pengrui; Lee, Jaemoon; Lynch, Joseph; Maligres, Peter; Molina, Audrey; Nemoto, Takayuki; Okada, Shigemitsu; Reamer, Robert; Song, Jake Z.; Tschaeen, David; Wada, Toshihiro; Zewge, Daniel; Volante, R. P.; Reider, Paul J.; Tomimoto, Koji
 CS Process R & D Laboratories for Technology Development, Banyu Pharmaceutical Co. Ltd., Okazaki Aichi, 444-0858, Japan
 SO Journal of Organic Chemistry (2001), 66(20), 6775-6786
 CODEN: JOCEAH; ISSN: 0022-3263
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 135:357830
 IT 203321-88-4P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of muscarinic receptor antagonist via a diastereoselective

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L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)
 Michael reaction, selective deoxyfluorination and arom. metal-halogen
 exchange reaction)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
 α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (uR)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

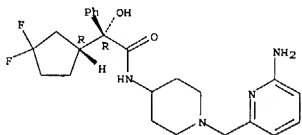


RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
 AB The pharmacol. profiles of
 (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (I), which is a novel muscarinic receptor antagonist with M2-sparing antagonistic activity, was evaluated. I inhibited [3H]NMS binding to cloned human muscarinic m1, m2, m3, m4, and m5 receptors expressed in Chinese hamster ovary cells with Ki values (nM) of 1.5, 540, 2.8, 15, and 7.7, resp. In isolated rat tissues, I inhibited carbachol-induced responses with 540 fold selectivity for trachea (KB = 1.2 nM) over atria (KB = 650 nM). In in vivo rat assays, I inhibited acetylcholine-induced bronchoconstriction and bradycardia with i.v. ED50 values of 0.022 and 510 mg/kg, resp. Furthermore, in dogs, I (0.1-1 mg/kg p.o.) dose dependently shifted the methacholine concentration-respiratory resistance curves. In mice, I (10 mg/kg i.v.) did not inhibit oxotremorine induced tremor. The brain/plasma ratio (KP) of I (3 mg/kg i.v.) was 0.13 in rats; this KP was less than scopolamine (1.7) and darifenacin (0.24). The inhibition of I (3 mg/kg i.v.) on ex vivo binding in rat cerebral cortex was almost similar to that of NMS. Therefore, I has high selectivity for M3 receptors over M2 receptors, displays a potent, oral M3 antagonistic activity without inhibition of central muscarinic receptors because of low brain penetration. It is well known that central muscarinic antagonists may have diverse CNS effects, and M2 receptors regulate cardiac pacing and act as autoreceptors in the lung and bladder. Thus, I may have fewer cardiac or CNS side effects than nonselective compds.
 AN 2001:321650 CAPLUS
 DN 135:132311
 TI Pharmacological properties of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide: a novel muscarinic antagonist with M2-sparing antagonistic activity
 AU Hirose, Hiroyasu; Aoki, Ikuro; Kimura, Toshifumi; Fujikawa, Toru; Numazawa, Tomoshige; Sasaki, Kaori; Sato, Akio; Hasegawa, Takuro; Nishikibe, Masaru; Mitsuura, Morihito; Ohtake, Norikazu; Mase, Tohiaki; Noguchi, Kazuhito
 CS Taikuba Research Institute, Banyu Pharmaceutical Co., Ltd., Ibaraki, Japan
 SO Journal of Pharmacology and Experimental Therapeutics (2001), 297(2), 790-797
 CODEN: JPETAB, ISSN: 0022-3565
 PB American Society for Pharmacology and Experimental Therapeutics
 DT Journal
 LA English
 IT 203321-88-4
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (pharmacol. properties of, as novel muscarinic antagonist with M2-sparing antagonistic activity)

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
 α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (uR)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

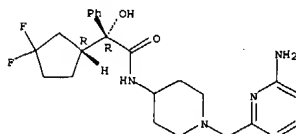


RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
 AB A medical condition in men known as Lower Urinary Tract Symptoms (LUTS)
 is treated by the administration of a muscarinic receptor antagonist in combination with at least one of a 5α-reductase inhibitor and an α-adrenergic receptor blocker.
 AN 2001:228701 CAPLUS
 DN 134:247264
 TI Treatment of lower urinary tract symptoms with muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors, and pharmaceutical compositions for use therein
 IN Stoner, Elizabeth; Drake, Paul J.; Bach, Mark A.
 PA Merck & Co., Inc., USA
 SO PCT Int. Appl., 20 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 PAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001021167	A1	20010329	WO 2000-US25534	20000918
W:				
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRAI US 1999-155357P	P	19990922		
OS MARPAT 134:247264				
IT 203321-88-4 331412-18-1 331412-19-2				
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (muscarinic and α-adrenergic antagonists and 5α-reductase inhibitors for treatment of lower urinary tract symptoms, and pharmaceutical compns.)				
RN 203321-88-4 CAPLUS				
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (uR)- (9CI) (CA INDEX NAME)				

Absolute stereochemistry. Rotation (+).



RN 331412-18-1 CAPLUS

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L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 1H-Indeno[5,4-f]quinoline-7-carboxamide, N-(1,1-dimethylethyl)-

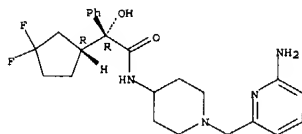
2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-4a,6a-dimethyl-2-oxo-,
(4aR,4bS,6aS,7S,9aS,9bS,11aR)-, mixt. with (αR)-N-[1-[(6-amino-2-
pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-
α-hydroxybenzeneacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 203321-88-4

CMF C24 H30 F2 N4 O2

Absolute stereochemistry. Rotation (+).

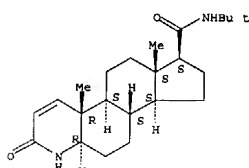


CM 2

CRN 98319-26-7

CMF C23 H36 N2 O2

Absolute stereochemistry.

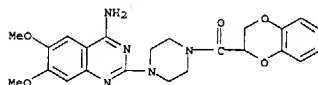


RN 331412-19 2 CAPLUS

CN 1H-Indeno[5,4-f]quinoline-7-carboxamide, N-(1,1-dimethylethyl)-

2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-4a,6a-dimethyl-2-oxo-,
(4aR,4bS,6aS,7S,9aS,9bS,11aR)-, mixt. with 1-(4-amino-6,7-dimethoxy-2-
quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazine
and
(αR)-N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

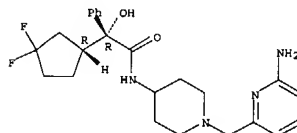
L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
3,3-difluorocyclopentyl]-α-hydroxybenzeneacetamide (9CI) (CA INDEX NAME)

CM 1

CRN 203321-88-4

CMF C24 H30 F2 N4 O2

Absolute stereochemistry. Rotation (+).

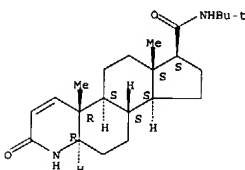


CM 2

CRN 98319-26-7

CMF C23 H36 N2 O2

Absolute stereochemistry.

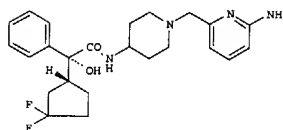


CM 3

CRN 74191-85-8

CMF C23 H25 N5 O5

L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
GI



AB Diastereoselective synthesis of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, a subunit of a novel muscarinic M3 receptor antagonist I (no biol. data presented), was achieved via Michael addition of an enolate of (2R,5R)-2-tert-butyl 5-phenyl-1,3-dioxolan-4-one to (-)-(3aS,4R,7S,7aR)-3a,4,7,7a-tetrahydro-4,7-methano-1H-inden-1-one in 90%

de as a key step.

AN 2000:854212 CAPLUS

DN 114:207688

TI Diastereoselective Synthesis of the Acid Part of a New Muscarinic M3 Receptor Antagonist

AU Mitauya, M.; Ogino, Y.; Ohtake, N.; Maue, T.

CS Banyu Tsukuba Research Institute in Collaboration with Merck Research Laboratories, Tsukuba, Ibaraki, 300-2611, Japan

SO Tetrahedron (2000), 56(51), 9901-9907

CODEN: TETRA8; ISSN: 0040-4020

Elsevier Science Ltd.

DT Journal

LA English

OS CASREACT 134:207688

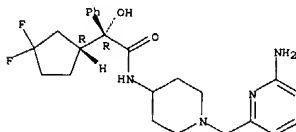
IT 203321-88-4P

RL: PNU (Preparation, unclassified); PREP (Preparation)
(diastereoselective prep of the benzeneacetamide subunit of a new muscarinic M3 receptor antagonist via stereoselective Michael addition and a retro Diels-Alder reaction)

RN 203321 88-4 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR) (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

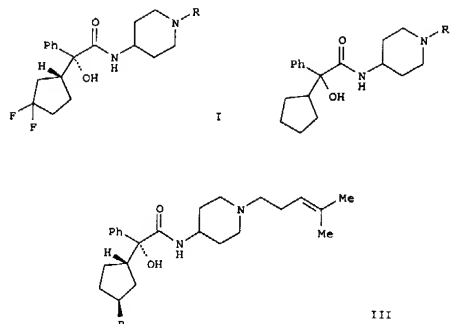


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L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

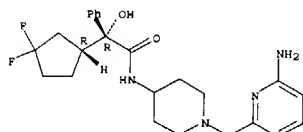
L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
GI



AB A novel series of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamides I (R = CH₂Ph, 3-furylmethyl, 2-pyridyl, etc.) and II (R = 2-MeC₆H₄CH₂, cyclohexylmethyl, 3-pyridylmethyl, etc.) was designed and synthesized based on the structure and biol. profiles of an active metabolite III (R = OH) of the prototype muscarinic M₃ receptor selective antagonist III (R = H), to develop a potent, long-acting, orally active M₃ antagonist for the treatment of urinary tract disorders, irritable bowel syndrome, and respiratory disorders. Investigation of I (R = (substituted phenyl)methyl, (substituted pyridyl)methyl, (substituted thienyl)methyl) containing a Ph or heterocyclic ring as the piperidinyl side chain in place of the 4-methyl-3-pentenyl moiety of I (R = 4-Me-3-pentenyl) revealed that this acid moiety was a versatile template for improving the selectivity for M₃ over M₂ receptors in comparison with the corresponding cyclopentylphenylacetic acid group. However, since the in vitro metabolic stability of these analogs was insufficient compared with that of III (R = OH), further derivatization was performed by introducing an appropriate hydrophilic group into the Ph or 2-pyridyl ring. Thus, the 1-(6-aminopyridin-2-ylmethyl)piperidine analog I (R = 6-amino-2-

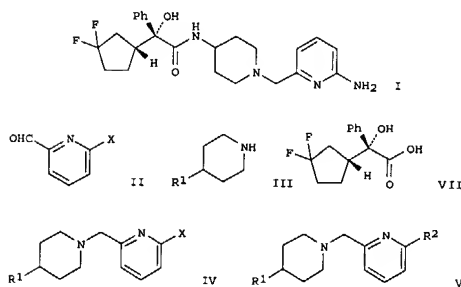
L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN (Continued)
pyridylmethyl) exhibiting 190-fold selectivity for M₃ receptors (K_i = 2.8 nM) over M₂ receptors (K_i = 530 nM) in a human binding assay and good in vitro metabolic stability in dog and human hepatic microsomes was identified. This compd. has excellent oral activity at 4 h after oral dosing (1 mg/kg), inhibiting methacholine-induced bronchoconstriction in dogs, and may be useful in clin. situations in which M₃ over M₂ selectivity is desirable.
AN 2000:832187 CAPLUS
DN 134:147471
TI A potent, long-acting, orally active
(2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; a novel muscarinic M₃ receptor antagonist with high selectivity for M₃ over M₂ receptors
AU Mitsuura, Morihiro; Kobayashi, Ken-ichi; Kawakami, Kumiko; Sato, Atsushi; Ogino, Yoshio; Kakikawa, Taro; Ohtake, Norikazu; Kimura, Toshifumi; Hirose, Hiroyasu; Sato, Akio; Numazawa, Tomoe; Hasegawa, Takuro; Noguchi, Kazuhito; Mase, Toshiaki
CS Banyu Tsukuba Research Institute in Collaboration with Merck Research Laboratories, Tsukuba, Ibaraki, 300-2611, Japan
SO Journal of Medicinal Chemistry (2000), 43(26), 5017-5029
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
IT 203321-88-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and muscarinic receptor antagonist activity of cyclopentylphenylacetamide derivative.)
RN 203321-88-4 CAPLUS
CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (αR)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2004 ACS ON STN
GI



AB An industrial process for the preparation of the title compds. (I) or salts thereof is characterized by reacting a compound of general formula (II); X = halo or a salt thereof with a compound of general formula (III); R₁ = optionally protected amino or a salt thereof under reducing conditions to obtain a compound of general formula (IV); X, R₁ = same as above) or salts thereof, reacting this compound or this salt with an aminating agent to obtain a compound of general formula (V); R₂ = optionally protected amino or a salt thereof, freeing at need the compound V or the salt thereof from the amino-protecting group of R₁ and the amino substituent of R₂ to obtain compound V (R₂ = NH₂) (VI) or a salt thereof, condensing the compound V or VI or the salt thereof with compound (VII), and removing the substituent of R₂. This process gives in high yields and fewer steps I which is known to exhibit highly selective antagonism against muscarinic M₃ receptor and to be useful for the treatment or prevention of respiratory, urinary, or digestive tract diseases (no data).

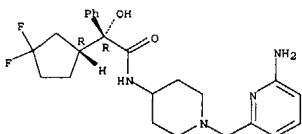
AN 2000:790497 CAPLUS
DN 133:350147
TI Processes for the preparation of piperidylmethylpyridine derivatives
IN Nemoto, Takayuki; Kawasaki, Masashi; Itoh, Takahiro; Mase, Toshiaki
PA Banyu Pharmaceutical Co., Ltd., Japan
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA Japanese

10688348

9/29/04

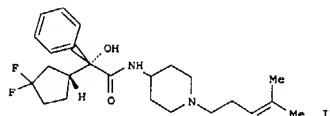
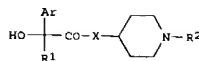
L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO 2000066579 A1 20001109 WO 2000-JP2755 20000426
 W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 PRAI JP 1999-123157 A 19990428
 OS CASREACT 133:350147; MARPAT 133:350147
 IT 203321-88-4P
 RL: IMP (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (process or preparation of piperidylmethylpyridine deriva. as muscarinic M3 receptor antagonists)
 RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-[(1R)-3,3-difluorocyclopentyl]-α-hydroxy-, (±R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 GI



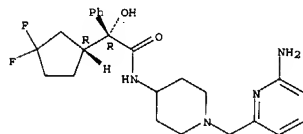
AB The title compds. (I; Ar = (un)substituted aryl or heteroaryl etc.; R1 = C1-3 cycloalkyl in which 1-4 arbitrary H may be substituted by F; R2 = saturated or unsatd., aliphatic C5-15 hydrocarbyl in which 1-6 arbitrary H may be substituted by F, alkyl, aralkyl, or heteroarylalkyl or heteroarylalkenyl having 1-2 heteroatoms selected from the group consisting of N, O, S; X = O, NH) or pharmaceutically acceptable salts thereof are prepared. Because of having selective muscarinic receptor antagonism and being excellent in oral activity, persistence of the action and dynamic in vivo, I are useful as efficacious and safe remedies or preventives with little side effects for respiratory, urol. and digestive diseases. Thus, (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid (preparation given) was reacted with 4-amino-1-(4-methyl-3-pentenyl)piperidine (preparation given) in the presence of 1,1'-carbonyldiimidazole and 4-dimethylaminopyridine to give the title compound (II), which showed ED50 of 0.033 mg/Kg against muscarinic receptor antagonism when tested with rat.

AN 1998:112344 CAPLUS
 DN 128:192550
 TI Preparation of fluorinated 1,4-disubstituted piperidine derivatives as muscarinic receptor antagonists
 IN Tauchiya, Yoshimi; Nomoto, Takashi; Ohsawa, Hirokazu; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
 PA Banyu Pharmaceutical Co., Ltd., Japan
 SO PCT Int. Appl., 115 pp.
 CODEN: PIXXDA
 DT Patent
 LA Japanese
 FAN.CNT 1

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI WO 9805641 A1 19980212 WO 1997-JP2600 19970728
 W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
 CA 2261680 A 19980212 CA 1997-2261680 19970728
 AU 9736351 A1 19980212 AU 1997-36351 19970728
 AU 716050 B2 20000217
 EP 930298 A1 19990721 EP 1997-93037 19970728
 EP 930298 B1 20021218
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
 BR 9711108 A 19990817 BR 1997-11108 19970728
 CN 1226888 A 19990825 CN 1997-196911 19970728
 TR 9900204 T2 20000121 TR 1999-9900204 19970728
 JP 2000169449 A2 20000620 JP 2000-27462 19970728
 JP 3282618 B2 20020520
 JP 2000178231 A2 20000627 JP 2000-27461 19970728
 JP 3282617 B2 20020520
 JP 3063164 B2 20000712 JP 1998-507794 19970728
 TR 200001482 T2 20001121 TR 2000 200001482 19970728
 NZ 333842 A 20010525 NZ 1997-333842 19970728
 AT 225941 E 20030115 AT 1997-933037 19970728
 ES 2188961 T3 20030701 ES 1997-933037 19970728
 US 5948792 A 19990907 US 1997-903768 19970731
 ZA 9706813 A 19980211 ZA 1997-6813 19970831
 KR 2000022214 A 20000425 KR 1998-710633 19981224
 NO 9900472 A 19990201 NO 1999-472 19990201
 US 6040449 A 20000321 US 1999-290607 19990413
 PRAI JP 1996-219436 A 19960801
 JP 1997-53979 A 19970221
 JP 1998-507794 A3 19970728
 WO 1997-JP2600 W 19970728
 US 1997 903768 A3 19970731
 OS MARPAT 128:192550
 IT 203321-30-6P 203321-31-7P 203321-42-0P
 203321-45-3P 203321-51-1P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of fluorinated 1,4-disubstituted piperidine deriva. as muscarinic receptor antagonists)
 RN 203321-30-6 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α-hydroxy-, dihydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

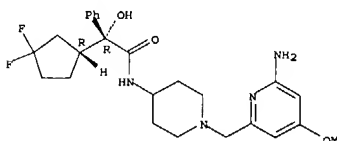
L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● 2 HCl

RN 203321-31-7 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-4-methoxy-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α-hydroxy-, dihydrochloride, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

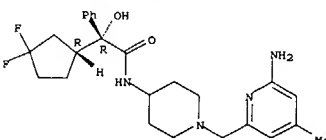
Absolute stereochemistry.



● 2 HCl

RN 203321 42-0 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-4-methyl-2-pyridinyl)methyl]-4-piperidinyl]-α-(3,3-difluorocyclopentyl)-α-hydroxy-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

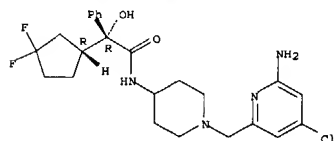


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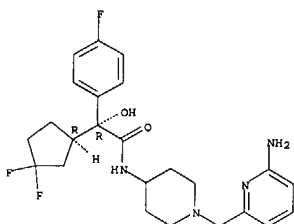
L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 RN 203321-45-3 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-4-chloro-2-pyridinyl)methyl]-4-piperidinyl]- α -(3,3-difluorocyclopentyl) α -hydroxy-, [R-(R*,R*)] (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 203321-51-1 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -(3,3-difluorocyclopentyl) 4-fluoro- α -hydroxy-, [R-(R*,R*)] (9CI) (CA INDEX NAME)

Absolute stereochemistry.

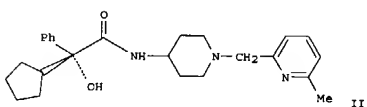
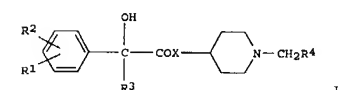


IT 203321-88-4P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation of fluorinated 1,4-disubstituted piperidine derivs. as muscarinic receptor antagonists)

RN 203321-88-4 CAPLUS
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -[(1R)-3,3-difluorocyclopentyl]- α -hydroxy-, (aR) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN
 GI



AB Substituted heteroatom. derivs. I [R1 and R2 are the same or different and

each represents hydrogen, halogeno or lower alkyl; R3 represents C3-6 cycloalkyl or cycloalkenyl; R4 represents heteroaryl having one or two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur atoms which may be fused with the benzene ring, provided that the heteroaryl is optionally substituted by lower alkyl, halogeno, lower alkoxy, amino or hydroxymethyl; and X represents O or NH] are prepared

The compds. are useful for the treatment of respiratory diseases (asthma, chronic respiratory obstruction, pulmonary fibrosis, etc.), urol. diseases

accompanied by urination disorders (frequent urination, urgency or micturition, urinary incontinence, etc.) and digestive diseases. In an

in vitro test for tracheal M3 receptor antagonism, the title compound II (preparation given) showed the KB value of 4.4 nM.

AN 1997:369690 CAPLUS

DN 126:343498

TI Preparation of substituted heteroatom derivatives as selective M3 muscarinic antagonists

MA: Masaki, Toshio; Mitsuura, Morihito; Kobayashi, Kenzuke; Noguchi, Kazuhito

PA Banyu Pharmaceutical Co., Ltd., Japan

SO PCT Int. Appl., 44 pp.

CODEN: PIKXD2

DT Patent

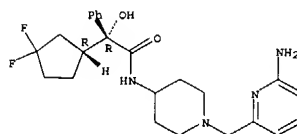
LA Japanese

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9713766	A1	19970417	WO 1996-JP2904	19961007
W:	AU, CA, CN, JP, KR, US			
RW:	AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,			
SE	CA 2234619	AA 19970417	CA 1996-2234619	19961007

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L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 AU 9671459 A1 19970430 AU 1996-71459 19961007
 EP 863141 A1 19980909 EP 1996-932827 19961007
 EP 863141 B1 20010912

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

AT 205490 E 20010915 AT 1996-932827 19961007
 US 6130232 A 20001010 US 1998-51287 19980409

PRAI JP 1995-291716 A 19951013
 JP 1995-351342 A 19951226
 WO 1996-JP2904 W 19961007

OS MARPAT 126:343498

IT 189819-56-5P 189819-57-6P

RL: BAC (Biological activity or effector, except adverse); BSU

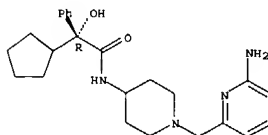
(Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of substituted heteroatom. derivs. as selective M3 muscarinic

antagonists)

RN 189819-56-5 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -cyclopentyl- α -hydroxy-, [R]- (9CI) (CA INDEX NAME)

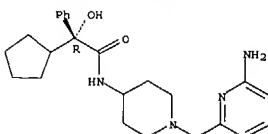
Absolute stereochemistry.



RN 189819-57-6 CAPLUS

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -cyclopentyl- α -hydroxy-, dihydrochloride, [R]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
116.00	271.63

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-16.80	-16.80

CA SUBSCRIBER PRICE

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CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 14:32:54 ON 29 SEP 2004

CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d his

(FILE 'HOME' ENTERED AT 14:29:44 ON 29 SEP 2004)

FILE 'REGISTRY' ENTERED AT 14:29:53 ON 29 SEP 2004

L1 STRUCTURE UPLOADED

L2 0 S L1

L3 14 S L1 FUL

FILE 'CAPLUS' ENTERED AT 14:30:22 ON 29 SEP 2004

L4 24 S L3

FILE 'USPATFULL, USPAT2' ENTERED AT 14:32:54 ON 29 SEP 2004

=> s l3

L5 6 L3

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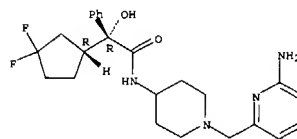
9/29/04

L5 ANSWER 4 OF 6 USPATFULL on STN
 AB In the production of fluorine-containing 1,4-disubstituted piperidine derivatives by the reaction of a carboxylic acid of formula where Ar represents aryl or heteroaryl and R.sub.10 represents C.sub.3 -C.sub.6 cycloalkyl in which up to 4 hydrogen atoms are substituted with fluorine or C.sub.3 -C.sub.6 cycloalkyl having 1 to 2 protected or unprotected hydroxyl or oxo groups, or a reactive derivative thereof, with a piperidine derivative of formula [IV] as defined in the specification, especially useful results are obtained using 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine or a salt thereof, e.g., trihydrochloride, as the piperidine derivative.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AN 2000:34693 USPATFULL
 TI Fluorine-containing 1, 4-disubstituted piperidine derivatives
 IN Tsuchiya, Yoshimi, Tsukuba, Japan
 Nomoto, Takashi, Menuma-machi, Japan
 Ohsawa, Hirokazu, Tsukuba, Japan
 Kawakami, Kumiko, Tsukuba, Japan
 Ohwaki, Kenji, Tsukuba, Japan
 Nishikibe, Masaru, Tsukuba, Japan
 PA Banyu Pharmaceutical Co Ltd, Tokyo, Japan (non-U.S. corporation)
 PI US 6040449 20000321
 AI US 1999-290607 19990413 (9)
 RLI Division of Ser. No. US 1997-903768, filed on 31 Jul 1997, now patented,
 Pat. No. US 5948792
 PRAI JP 1996-219436 19960801
 JP 1997-53979 19970221
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Chang, Ceila
 CLMN Number of Claims: 2
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 2481

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 IT 203321-30-6P
 (preparation of fluorinated 1,4-disubstituted piperidine deriva. as muscarinic receptor antagonists)
 RN 203321-30-6 USPATFULL
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -(3,3-difluorocyclopentyl)- α -hydroxy-, dihydrochloride, [R-(R*,R*)]-(9CI) (CA INDEX NAME)
 Absolute stereochemistry. Rotation (+).

L5 ANSWER 4 OF 6 USPATFULL on STN (Continued)



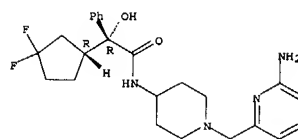
● 2 HCl

L5 ANSWER 5 OF 6 USPATFULL on STN
 AB Novel fluorine-containing 1,4-disubstituted piperidine derivatives, represented by general formula [I] ##STR1## such as, for example, (2R)-N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide or pharmaceutically acceptable salt thereof, are potent and selective antagonists for muscarinic M.sub.3 receptors with little side effects. The compounds of formula [I] exhibit excellent oral activity, duration of activity and pharmacokinetics. They are useful for treatment and prophylaxis of respiratory diseases, such as chronic obstructive pulmonary diseases; urinary diseases, such as urinary incontinence; and digestive diseases, such as irritable bowel syndrome, and motion sickness.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AN 1999:106468 USPATFULL
 TI Fluorine containing 1,4-disubstituted piperidine derivatives
 IN Tsuchiya, Yoshimi, Tsukuba, Japan
 Nomoto, Takashi, Menuma-machi, Japan
 Ohsawa, Hirokazu, Tsukuba, Japan
 Kawakami, Kumiko, Tsukuba, Japan
 Ohwaki, Kenji, Tsukuba, Japan
 Nishikibe, Masaru, Tsukuba, Japan
 PA Banyu Pharmaceutical Co., Ltd., Tokyo, Japan (non U.S. corporation)
 PI US 5948792 19990907
 AI US 1997-903768 19970731 (8)
 PRAI JP 1996-219436 19960801
 JP 1997-53979 19970221
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Chang, Ceila
 LREP Sherman and Shalloway
 CLMN Number of Claims: 23
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 2821

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 IT 203321-30-6P
 (preparation of fluorinated 1,4-disubstituted piperidine deriva. as muscarinic receptor antagonists)
 RN 203321-30-6 USPATFULL
 CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]- α -(3,3-difluorocyclopentyl) α -hydroxy-, dihydrochloride, [R-(R*,R*)]-(9CI) (CA INDEX NAME)
 Absolute stereochemistry. Rotation (+).

L5 ANSWER 5 OF 6 USPATFULL on STN (Continued)



● 2 HCl

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L5 ANSWER 6 OF 6 USPAT2 on STN
AB An improved and efficient synthesis for the preparation of
2-amino-6-[(4-aminopiperidin-1-yl)methyl]pyridine, an intermediate
compound in the preparation of muscarinic M3 receptor antagonists,
includes as a final step the removal of trimethylacetyl and an amino
protecting group from 2-trimethylacetyl-amino-6-[(4-protected
aminopiperidin-1-yl)methyl]pyridine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AN 2001:229774 USPAT2
TI Process for the preparation of chemical compounds
IN Malignes, Peter E., Fanwood, NJ, United States
Lee, Jaemoon, Edison, NJ, United States
PA Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
PI US 6469172 B2 20021022
AI US 2001 799440 20010305 (9)
PRAI US 2000-187816P 20000308 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Covington,
Raymond
LREP Yang, Mollie M., Rose, David L.
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 614

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

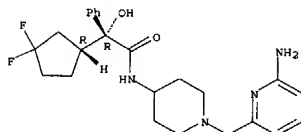
IT 203321-88-4P

(preparation of piperidine derivs.)

RN 203321-88-4 USPAT2

CN Benzeneacetamide, N-[1-[(6-amino-2-pyridinyl)methyl]-4-piperidinyl]-
 α -[(1R)-3,3-difluorocyclopentyl]- α -hydroxy-, (4R)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

35.30

306.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

0.00

-16.80

STN INTERNATIONAL LOGOFF AT 14:33:22 ON 29 SEP 2004